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Original Article

Brainstem infarction and sleep-disordered breathing in the BASIC sleep apnea study ☆

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ABSTRACT

Background: Association between cerebral infarction site and poststroke sleep-disordered breathing (SDB) has important implications for SDB screening and the pathophysiology of poststroke SDB. Within a large, population-based study, we assessed whether brainstem infarction location is associated with SDB presence and severity.

Methods: Cross-sectional study was conducted on ischemic stroke patients in the Brain Attack Surveillance in Corpus Christi (BASIC) project. Subjects underwent SDB screening (median 13 days after stroke) with a well-validated cardiopulmonary sleep apnea-testing device ($n = 355$). Acute infarction location was determined based on review of radiology reports and dichotomized into brainstem involvement or none. Logistic and linear regression models were used to test the associations between brainstem involvement and SDB or apnea/hypopnea index (AHI) in unadjusted and adjusted models.

Results: A total of 38 participants (11%) had acute infarction involving the brainstem. Of those without brainstem infarction, 59% had significant SDB (AHI $\geqslant$ 10); the median AHI was 13 (interquartile range (IQR) 6, 26). Of those with brainstem infarction, 84% had SDB; median AHI was 20 (IQR 11, 38). In unadjusted analysis, brainstem involvement was associated with over three times the odds of SDB (odds ratio (OR) 3.71 (95% confidence interval (CI): 1.52, 9.13)). In a multivariable model, adjusted for demographics, body mass index (BMI), hypertension, diabetes, coronary artery disease, atrial fibrillation, prior stroke/transient ischemic attack (TIA), and stroke severity, results were similar (OR 3.76 (95% CI: 1.44, 9.81)). Brainstem infarction was also associated with AHI (continuous) in unadjusted ($p = 0.004$) and adjusted models ($p = 0.004$).

Conclusions: Data from this population-based stroke study show that acute infarction involving the brainstem is associated with both presence and severity of SDB.

1. Introduction

Sleep-disordered breathing (SDB) predicts both incident ischemic stroke [1–3] and poor outcomes after stroke, including functional impairment and mortality [4,5]. As SDB affects more than half of all patients after stroke [6], it represents an important determinant of outcomes. However, the reason for the high prevalence after stroke is poorly understood. The known risk factors for SDB in the general population, such as male sex, body mass index (BMI), and SDB symptoms, do not appear to be potent predictors of SDB in the poststroke population [7,8]. Whether SDB more often precedes stroke or results from it remains uncertain [9]. Given the association between dysphagia and poststroke SDB [10], and control of both upper airway tone and regulation of breathing by the brainstem, infarctions that affect this region rather than supratentorial or cerebellar locations might be hypothesized to show stronger associations with SDB. However, previous efforts to clarify whether brainstem infarcts in comparison to other locations are more likely to show associations with SDB have been hampered

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by a small sample size (the largest of these included 97 subjects with brain infarction) [11–13] or were limited to a single race with narrow enrollment criteria [14], and have not produced a consistent answer. A better understanding of the pathophysiology of poststroke SDB could have important implications for its diagnosis, treatment, and prevention.

To overcome previous barriers and clarify whether brainstem location of ischemic stroke is associated with poststroke SDB, we added objective assessment of SDB to a population-based stroke study. We hypothesized that brainstem infarction would be associated with the presence and severity of poststroke SDB. As a secondary aim, we also assessed whether infarct size is associated with risk of poststroke SDB.

2. Methods

Ischemic stroke patients were identified through the Brain Attack Surveillance in Corpus Christi (BASIC) study. This population-based stroke surveillance study identifies all cases of stroke in Nueces County through active and passive surveillance, in those who are age 45 or greater and who are Nueces County residents. The geographic isolation of this community, sparsely populated surrounding areas, and lack of an academic medical center allow for complete case capture for stroke without referral bias. Detailed methods have been published previously [15–17]. Ischemic stroke was defined based on a traditional clinical definition as an acute onset of focal neurological deficit specifically attributable to a cerebrovascular distribution that persists for >24 h (except in cases of sudden death or if the development of symptoms is interrupted by a surgical or interventional procedure), thought to be due to cerebral ischemia and not attributable to another disease process, such as seizure, brain tumor, hypoglycemia, metabolic encephalopathy, or hysteria [18]. Thus, acute infarction was not required for the ischemic stroke definition. Each diagnosis was validated by study neurologists with the use of source documents including emergency department records, history and physical exams, progress notes, neurology consultation notes, and neuroimaging records [16]. Each subject had medical history, including height and weight, abstracted, under standardized procedures, from the index stroke hospitalization's paper or electronic medical record by trained study personnel. The National Institutes of Health Stroke Scale (NIHSS) was obtained directly from the medical record or abstracted by standard methods [19]. Baseline interviews were performed with each subject or a proxy. Head computed tomography (CT) and brain magnetic resonance image (MRI) reports of studies performed during the acute stroke hospitalization were reviewed by board-certified neurologists, masked to the sleep apnea information, for location of acute infarction and coded as brainstem involved or not. Location within the brainstem was also qualified. Size of acute infarction was categorized as <1.5 cm (consistent with a potential lacunar mechanism), $\geqslant$1.5 cm, unclear size of single infarction, multiple infarctions, and no infarction.

Subjects enrolled in the parent BASIC project were offered SDB assessment with the ApneaLink Plus™. Exclusion criteria included use of supplemental oxygen, current mechanical ventilation or other positive pressure ventilation, or pregnancy. Studies were performed within 30 days of stroke onset if identified by active surveillance and 45 days from onset if identified by passive surveillance.

The ApneaLink Plus™, a well-validated [20–27] cardiopulmonary device designed to assess for obstructive sleep apnea, monitors nasal pressure (airflow), oxygen saturation, pulse, and respiratory effort (chest excursion). SDB was defined conservatively by an apnea/hypopnea index (AHI) $\geqslant$10, as Apnealink™ validation studies, with use of the ApneaLink's default settings (see below), have shown nearly perfect sensitivity and specificity for SDB with this cutoff (example: sensitivity 0.98, specificity 1.0) [24]. The correlation in AHI between ApneaLink™ Plus and full polysomnography is 0.97 [28].

The decision to use out-of-center sleep apnea testing as opposed to laboratory polysomnography was made because the latter is not a realistic option in a large, community-based study of patients with acute stroke [8,29]. Key goals of this research were to enroll the largest community sample yet studied, and secure a high participation rate. Detection of pathophysiological apneas and hypopneas with cardiopulmonary sleep apnea monitoring systems has become sufficiently accurate to allow increasing use in clinical practice. We and others have previously shown that full polysomnography is not often feasible in the acute stroke setting, and we anticipated that in the present study, a sizable number of otherwise eligible subjects would have been lost had we used it [8,29].

The primary SDB measure, the AHI, generated by the ApneaLink Plus™ is considered quite accurate [20–28]. Some misclassifications may occur between central and obstructive events captured within the overall AHI. Nonetheless, in clinical practice, obstructive sleep apneas are often accompanied by some central apneas as well; treatment is usually guided by the overall AHI and first-line treatment for predominantly obstructive or central apnea is usually the same, in each case with positive airway pressure. Several studies have now established that central sleep apnea is a relatively small contributor to SDB post stroke [5,8,29,30]. In any case, the correlation between the ApneaLink Plus™ central sleep apnea index and that generated by polysomnography is reasonably high (correlation coefficient 0.94) [28]. Therefore, for the present study in which community-based assessment of overall SDB and its relation to brainstem stroke were the key priority, we used out-of-center sleep apnea testing and addressed questions about central versus obstructive SDB etiologies only in secondary analyses.

Recordings were reviewed by a registered polysomnographic technologist, who was masked to the imaging results and study hypothesis, to eliminate artifacts and presumed wakeful times, and to adjust any inappropriately scored events. Consistent with ApneaLink's default settings used in validation studies, apneas were defined by at least 80% decrease in nasal pressure compared to baseline for at least 10 s. Consistent with the AASM 2007 guidelines, an hypopnea was identified by at least 30% decrease in nasal pressure for at least 10 s, if followed by a 4% or greater oxygen desaturation, or, if oximetry data were missing for a significant portion of recording, as occurred in 6% of recordings, an hypopnea was defined as a reduction in nasal pressure of at least 50% for at least 10 s [31]. ApneaLink Plus™ software tabulated the AHI, the sum of all apneas plus hypopneas per hour of recording, in addition to secondary measures of the central apnea index (central apneas per hour), obstructive apnea index (obstructive apneas per hour), and the hypopnea index (hypopneas per hour).

2.1. Statistical methods

Demographics and baseline characteristics were summarized with descriptive statistics. Logistic regression was used to test the association between brainstem infarction location and SDB. The *C*-statistic was calculated as a measure of discrimination for the unadjusted model to demonstrate the degree to which brainstem infarction alone predicts SDB. Linear regression was used to test the association between brainstem involvement and AHI. Because AHI was skewed, the natural log of AHI plus one was used as the outcome. Models were performed unadjusted and adjusted for the following prespecified potential confounders: age, sex,

race/ethnicity, BMI, hypertension, diabetes, coronary artery disease, atrial fibrillation, prior stroke/TIA, and NIHSS. These models were repeated after exclusion of patients without an area of acute infarction. To assess the overall association between infarction size and SDB, logistic regression models with the aforementioned potential confounders were compared with and without the infarction size variables (modeled as a series of four dummy variables with <1.5 cm as the referent) with a likelihood ratio test ($X^2_{df=4}$). Similar comparisons were made with an *F*-test for linear models with AHI as the outcome. To test the association between presence of an acute infarction of any size (referent clinical stroke without associated acute infarction) and SDB or AHI, unadjusted and adjusted logistic and linear regression models were built including the covariates described above. Subjects of American Indian race who were non-Hispanic were excluded from the models due to small numbers ($n = 5$). Statistical analyses were performed with TIBCO Spotfire S + ® 8.1 for Windows or R version 2.13.1. Institutional Review Boards of the University of Michigan and Corpus Christi hospital systems approved this project. Written informed consent was obtained from each subject or a proxy.

3. Results

Of 684 ischemic stroke subjects interviewed in BASIC, 515 met eligibility criteria for SDB testing. Of the 378 (73%) who consented and had ApneaLink Plus™ studies performed consecutively between 9/8/10 and 3/7/13, 23 had insufficient ApneaLink Plus™ data because of insufficient duration or quality of the recording. The remaining 355 subjects are included in this analysis. Their baseline characteristics, by brainstem infarction status, are given in Table 1. Subjects with brainstem infarction were younger and had a higher prevalence of diabetes. Although no other statistical differences in baseline characteristics were identified, intravenous tpa administration, dyslipidemia, coronary disease, atrial fibrillation, and excessive alcohol use appeared more common in those without brainstem infarction. Median time from stroke symptom onset to SDB assessment was 13 days (IQR: 6, 21) overall, with no difference by SDB status ($p = 0.24$). Median time from stroke symptom onset to SDB assessment was earlier (8 days (IQR: 3, 17)) in those with brainstem infarction compared with those without brainstem infarction (13 days (IQR: 6, 21), $p = 0.01$. No difference ($p = 0.56$) in median AHI was identified in those with an early (AHI: 15 (IQR: 6, 27)) versus late (AHI: 13 (IQR: 6, 27)) SDB assessment, based on a median split. Most ($n = 323$, 91%) had a brain MRI performed; the remainder only had CT scans ($n = 32$, 9%). At least one acute infarction was identified in 285 (80%). Of those without an acute infarction, 24% had only CT imaging. Brainstem infarction occurred in 38 (11%) of all subjects. Of these, four (11%) had at least one additional area of infarction outside of the brainstem. Of those without brainstem infarction ($n = 317$), 95 (30%) had multiple acute infarctions. Of the brainstem infarctions, 30 infarctions involved the pons, seven the midbrain, three the medulla, and one was unclear. Among the 38 subjects, three had infarctions that spanned multiple brainstem locations (both the pons and medulla). The prevalence of SDB was 84% in those with and 59% in those without brainstem infarction. The median AHI was 20 (IQR: 11, 38) in those with and 13 (IQR: 6, 26) in those without brainstem infarction. Central apnea and hypopnea indices were demonstrably higher in those with brainstem infarction, while the obstructive apnea index was not (Table 2). Those with pontine and medullary infarctions had the highest nominal AHI (Table 2), followed by those with midbrain infarctions, but statistical comparisons were precluded by small sample sizes.

3.1. Brainstem infarction model results

In unadjusted analysis, brainstem infarction was associated with over three times the odds of SDB (odds ratio (OR) 3.71 (95% confidence interval (CI): 1.51, 9.13). The *C*-statistic for this unadjusted model was 0.55. In a multivariable model, results were similar to an OR of 3.76 (95% CI: 1.44, 9.81). Brainstem infarction was associated with AHI in unadjusted (beta = 0.45, $p = 0.004$) and adjusted models (beta = 0.43, $p = 0.004$). However, given an adjusted R^2 of 0.021 in the unadjusted model, only approximately 2% of the variance of AHI was accounted for by brainstem location.

With exclusion of subjects without an acute infarction from the data set, brainstem infarction was still associated with over three times the odds of SDB in unadjusted (OR 3.34 (1.35, 8.30)) and adjusted (OR 3.29 (1.24, 8.73)) analyses. The association between brainstem infarction and AHI also persisted (unadjusted model: beta = 0.41, $p = 0.01$; adjusted model: beta = 0.38, $p = 0.01$).

Table 1
Baseline characteristics of ischemic stroke patients ($n = 355$) with and without brainstem infarction.

	Brainstem infarction ($n = 38$) *N* (%) or median (IQR)	No brainstem infarction ($n = 317$) *N* (%) or median (IQR)
Age*	60 (57, 71)	66 (58, 77)
Race/ethnicity		
Non-Hispanic white	8 (21)	117 (37)
Mexican American	28 (74)	182 (57)
Am Indian	0 (0)	5 (2)
Black	2 (5)	13 (4)
Male	21 (55)	176 (56)
Hypertension	32 (84)	259 (82)
Dyslipidemia	16 (42)	157 (50)
Prior stroke/TIA	11 (29)	84 (27)
Diabetes*	24 (63)	142 (45)
Coronary disease	8 (21)	91 (29)
Atrial fibrillation	1 (3)	40 (13)
Current smoker	10 (26)	72 (23)
Excessive alcohol	1 (3)	46 (15)
NIHSS	3 (2, 5)	4 (2, 7)
Body mass index	29 (25, 36)	28 (25, 32)
IV tpa	1 (3)	37 (12)

NIHSS: National Institutes of Health Stroke Scale.
* $p < 0.05$.

Table 2
Sleep-disordered breathing indices, presented as medians and interquartile ranges, in ischemic stroke subjects ($n = 355$) with and without brainstem infarction.

	Apnea–hypopnea index	Obstructive apnea index	Central apnea index	Hypopnea index
Brainstem infarction ($n = 38$)	20 (11, 38)	3 (1, 11)	1 (0, 3)	11 (6, 15)
No brainstem infarction ($n = 317$)	13 (6, 26)	3 (1, 10)	0 (0, 0)	6 (2,12)
p value	0.007	0.622	0.04	0.002
Midbrain infarction only ($n = 7$)	22 (19, 44)	6 (2, 14)	2 (0, 4)	17 (9, 22)
Pontine infarction only ($n = 27$)	16 (11, 35)	2 (1, 10)	1 (0, 3)	10 (6, 14)
Pontine and medullary infarction ($n = 3$)	37 (24, 38)	7 (4, 15)	1 (1, 4)	15 (13, 19)

3.2. Infarction size and presence model results

Prevalence and severity of SDB are presented by infarction size in Table 3. Size of infarction was not associated with SDB ($X^2_{df=4} = 5.5$, $p = 0.24$) or AHI ($F = 0.82$, $p = 0.51$). While presence of an acute infarction of any size (referent: no acute infarction) was associated with the presence of SDB in unadjusted analysis (OR 1.82 (95% CI: 1.07, 3.11)), it was not in the multivariable model (OR 1.73 95% CI: 0.97, 3.09).

4. Discussion

This population-based study shows that presence of an acute infarction in the brainstem is associated with both presence and severity of SDB. These results were found despite a higher age, a factor typically associated with a higher risk of SDB in the general population, in those without brainstem infarction. The SDB prevalence of 84% in those with and 59% in those without brainstem infarctions greatly exceeds that found among age-matched controls for a prior stroke study (23% in men and 14% in women) [32]. While a causal association between infarction location and SDB is not proven by this study, SDB is not hypothesized to increase the risk of infarction in the brainstem more so than other areas, given the putative mechanisms by which SDB could contribute to stroke [33]. Thus, the association between infarction location and poststroke SDB more likely suggests that breathing during sleep can be dysregulated as a result of a brainstem stroke. At the same time, given that the predictive value of brainstem infarction for SDB (C-statistic 0.55) was not strong, the findings do not eliminate the likelihood that SDB often does predate stroke. Similarities between SDB prevalence after stroke and TIA [8], and the lack of association between stroke severity and SDB in small studies [12,34] also support the hypothesis that SDB often predates stroke. In any case, current results have important implications for clinical practice. Although the argument can be made for SDB screening in any poststroke patient, evaluation may be particularly important in patients who have had brainstem strokes, in any location of the brainstem. Moreover, the notable success of out-of-center sleep apnea testing for these patients – nearly 70% of eligible subjects agreed to testing and generated sufficient data – indicates that screening with these studies, at least in the acute poststroke period, may be a more effective strategy in practice than traditional polysomnography. In fact, most research investigations of poststroke sleep apnea do not use polysomnography [5,6,14,35–37].

Table 3
Prevalence and severity of sleep-disordered breathing by infarction size.

	Sleep-disordered breathing n (%)	Median AHI (IQR)
<1.5 cm ($n = 73$)	51 (70)	16 (7, 24)
⩾1.5 ($n = 74$)	47 (64)	16 (6, 32)
Unclear size ($n = 39$)	26 (67)	15 (8, 26)
Multiple ($n = 99$)	60 (61)	14 (7, 28)
No infarction ($n = 70$)	34 (49)	9 (4, 22)

AHI: apnea/hypopnea index.

A few smaller studies have examined the relationship between SDB and infarction location. One study in the acute stroke period showed that 13 subjects with brainstem infarction had SDB, defined by AHI ⩾ 10 with a portable respiratory monitor, at a frequency that was similar to that found among 81 patients with hemispheric infarction [11]. Another study showed a nonsignificant increase in AHI among 11 patients with infratentorial infarction as compared to 28 with supratentorial infarction [12]. A third report of three patients with brainstem infarction suggested that they appeared to have more central apneas, as a percent of total apneas, than did 16 patients with hemispheric stroke [13]. Among patients with lacunar infarction, infarctions of the internal capsule and pons, as opposed to the basal ganglia, centrum semiovale, and thalamus, were associated with a higher prevalence of SDB (AHI ⩾ 10) [38]. Differences between our findings and these previous reports may reflect our larger sample size and ability to detect smaller differences. However, a larger study ($n = 293$) performed in Korea found no difference in AHI across locations, including the brainstem [14]. The disparate findings may result from their exclusion of patients with decreased level of consciousness on admission or possible differences in the pathophysiology of poststroke SDB based on race/ethnicity. For instance, Asians may have an anatomic predisposition to SDB compared with Caucasians [39].

If SDB were the direct result of stroke, worse SDB might be anticipated in those with larger infarctions. However, this study corroborated that size of infarction was not associated with either presence or severity of SDB. Consistent with our findings, one study of 47 acute stroke patients found no association between SDB (AHI ⩾ 10) and infarction size, measured by volume or area [34]. Similarly, no association was identified between lack of acute infarction and absence of SDB [34]. Another recently published larger study showed no difference in AHI between those with a large hemispheric infarction and those with a small subcortical infarction [14].

Strengths of this study include its size, population-based sample, and use of objective measures for both outcomes and key explanatory variables. However, some limitations should also be considered. As less severe strokes were common in our patients due to our population-based design, our results may not be generalizable to patients with severe stroke. However, our sample was representative of the overall BASIC population with respect to demographics, stroke risk factors, and stroke severity, which increases generalizability to the community. Medical history abstracted from the medical record was limited to the index hospitalization, and sample size may have been insufficient to demonstrate differences in medical history by infarction location status. Furthermore, because of the study size, we were able to use multivariable modeling to adjust for many important potential confounders, such as stroke severity, though residual confounding or unmeasured confounding could still exist. We may have lacked the power to identify an association between infarction of any size and SDB in the adjusted model, given the borderline association found. This study was performed in a bi-ethnic community so

the results may not be representative of other communities with a different racial/ethnic composition. Our use of the ApneaLink Plus™ rather than laboratory-based polysomnography, though essential to answer the main research question for this study, may have limited our ability to distinguish central versus obstructive apneas and did not allow us to differentiate between central and obstructive hypopneas. MRI was not performed on every patient, though all cases of stroke were validated by study neurologists using standardized definitions. Presumably, this more accurately reflects clinical practice in which not every patient undergoes or can undergo an MRI. We reviewed imaging reports and not the actual imaging studies, thus misclassification is possible. Without access to the actual studies, we were also unable to calculate infarction volume. Finally, as the prevalence of SDB was high in this and other samples of stroke patients, the prevalence OR should not be interpreted as the relative risk.

Data from this large, population-based study with objective measures for both SDB and stroke indicate that infarct location in the brainstem is associated with more severe SDB. Although the relationship identified does not obviate the need to consider SDB in all acute stroke patients, the findings do provide some new support for the hypothesis that acute brainstem stroke can be a contributor to SDB. The high degree of overlap between stroke and SDB highlights the need for further research into mechanisms that underlie the comorbidity and effective strategies to identify and alleviate the impact of SDB as effectively as possible.

Conflict of interest

The ICMJE Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2014.04.003.

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